

Detection of Coronary Artery Disease in Asymptomatic Patients With Type 2 Diabetes Mellitus

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OBJECTIVES	We sought to verify the effectiveness of current American Diabetes Association screening guidelines in identifying asymptomatic patients with coronary artery disease (CAD) in type 2 diabetes mellitus (DM2).
BACKGROUND	In DM2 patients, CAD generally is detected in an advanced stage with an extensive atherosclerosis and poor outcome, whereas CAD in an asymptomatic stage is commonly missed.
METHODS	This study included 1,899 asymptomatic DM2 patients (age ≤ 60 years). Of these, 1,121 had ≥ 2 associated risk factors (RFs), group A, and the remaining 778 had ≤ 1 RF, group B, for CAD. All patients underwent dipyridamole myocardial contrast echocardiography (MCE), and in those with myocardial perfusion defects, the anatomy of coronary vessels was analyzed by selective coronary angiography.
RESULTS	In the two study groups, the prevalence of abnormal MCE (59.4% vs. 60%, $p = 0.96$) and of a significant CAD (64.6% vs. 65.5%, $p = 0.92$) was similar, irrespective of RF profile. But coronary anatomy differed: group B had a lower prevalence of three-vessel disease (7.6% vs. 33.3%, $p < 0.001$), of diffuse disease (18.0% vs. 54.9%, $p < 0.001$), and of vessel occlusion (3.8% vs. 31.2%, $p < 0.001$), whereas one-vessel disease was more frequent (70.6% vs. 46.3%, $p < 0.001$). Coronary anatomy did not allow any revascularization procedure in 45% of group A patients.
CONCLUSIONS	An "aggressive" diagnostic approach, requiring coronary angiography in asymptomatic DM2 patients with ≤ 1 associated RF for CAD and abnormal MCE, identified patients with a subclinical CAD characterized by a more favorable angiographic anatomy. The criterion of ≥ 2 RFs did not help to identify asymptomatic patients with a higher prevalence of CAD and is only related to a more severe CAD with unfavorable coronary anatomy. (J Am Coll Cardiol 2006;47:65–71) © 2006 by the American College of Cardiology Foundation

Diabetes is an important risk factor for the development of CAD (1). It has been estimated that 75% of the deaths in diabetic patients may be attributed to CAD (2). Patients with diabetes develop CAD at an accelerated rate and have a higher incidence of heart failure, myocardial infarction, and cardiac death than their nondiabetic counterparts (3). In general, CAD in diabetic patients is detected in an advanced stage, whereas the disease in its premature, asymptomatic stages remains unfortunately undetected (4). As a consequence, diabetic patients have a more extensive coronary atherosclerosis and their epicardial vessels are less amenable to interventional treatment compared with the nondiabetic population (5–7). Moreover, compared with nondiabetic patients, diabetic subjects have lower ejection fraction and more frequent silent myocardial infarction (8–13). These findings might easily explain the poor outcome of these patients. Such observations impose an aggressive approach to diagnostic strategies in diabetic patients to detect CAD in an early asymptomatic stage, which is probably characterized by a more favorable coronary vessel anatomy and by

the absence of significant myocardial complications. The Consensus Development Conference on the diagnosis of CAD in people with diabetes of the American Diabetes Association (ADA) (14) recommends performing stress screening for CAD in asymptomatic patients with two or more additional risk factors (RFs). It was stated that asymptomatic diabetic patients with ≤ 1 RF do not require cardiac testing. These indications were not on the basis of clinical data, which are lacking, but rather on the personal judgments and consensus of experts.

In the present study, including a large population of adult (age ≤ 60 years) asymptomatic patients with type 2 diabetes mellitus (DM2), we used a diagnostic approach of a coronary angiogram after the demonstration of myocardial perfusion defects by stress myocardial contrast echocardiography (MCE), which has been shown to accurately assess flow-limiting coronary artery stenosis during vasodilator tests (15,16). Each patient completed the diagnostic sequence irrespective of the RF profile. The purpose was to verify the effectiveness of current ADA screening guidelines in identifying asymptomatic patients with CAD. These guidelines are on the basis of the assumption (never previously demonstrated) that asymptomatic DM2 patients with more RFs are more likely to have significant CAD than

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Abbreviations and Acronyms

ADA	= American Diabetes Association
beta	= rate constant
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
CVD	= cardiovascular disease
DM2	= type 2 diabetes mellitus
HbA	= hemoglobin
LAD	= left anterior descending coronary artery
LCX	= left circumflex coronary artery
MBF	= myocardial blood flow
MCE	= myocardial contrast echocardiography
MBV	= myocardial blood volume
PCI	= percutaneous coronary intervention
RF	= risk factor

those with fewer RFs and, thus, more likely to have abnormal stress imaging abnormalities. Furthermore, we investigated whether the aggressive diagnostic approach proposed in this study has the same capacity of identifying asymptomatic patients with significant CAD, with the advantage of detection in a phase with a more favorable angiographic anatomy that might render the coronary vessels more amenable to interventional treatment.

METHODS

Patients and study design. The population of the province of Padua is served by a unified medical care system that has accumulated comprehensive records over a long period of time and has a relatively high diabetes mellitus prevalence. Each care unit for diabetic patients in the country uses a medical record system whereby all data are assembled in one place (Diabetes Care Unit of Padua University). For this study, all consecutive diabetic patients who had a follow-up visit in the first three-month period of 2003 were included. The flow chart of the study population is depicted in Figure 1. This prospective study enrolled 2,437 consecutive,

asymptomatic patients with DM2 (age ≤ 60 years). Forty-two patients refused to participate, and 449 were excluded because they have angina pectoris or anginal-equivalent symptoms or a previous history of angina subsequently resolved. To exclude patients with high risk of complications during dipyridamole stress, established CAD, or entities potentially associated with perfusion defects, the following exclusion criteria were adopted: 1) previous history of bronchial asthma precluding the use of dipyridamole; 2) history of documented myocardial infarction; 3) electrocardiographic evidence of Q-wave myocardial infarction, ischemic ST-segment, or T-wave changes; 4) prior percutaneous coronary intervention or coronary artery bypass grafting; 5) technically suboptimal contrast echocardiographic images; and 6) clinically significant valvular heart disease or cardiomyopathy. On the basis of these criteria, 47 patients were excluded.

At the beginning of the study, the RFs considered were those outlined in 1998 by Consensus Statement of the ADA (14). The targets for these RFs were subsequently re-evaluated after the publication of the last (2005) Position Statement in Standards of medical care in diabetes (17) (i.e., low-density lipoprotein [LDL] cholesterol ≥ 100 mg/dl or high-density lipoprotein [HDL] cholesterol < 40 mg/dl, blood pressure $\geq 130/80$ mm Hg, smoking, family history of premature CAD [defined by ascertained critical epicardial coronary atherosclerosis, sudden cardiac death with coronary atherosclerosis at autopsy, or myocardial infarction in a family member younger than 45 years in men and younger than 55 years in women], and positive micro/macroalbuminuria), whereas criteria to indicate a stress test to detect silent CAD remain unchanged (14). Statistical analysis of data collected did not show significant differences in any of the evaluated hypotheses independently on the criteria used (ADA, 1998 vs. 2005). Hence, we referred the results derived only from data analysis obtained in light of 2005 ADA standards of care (17).

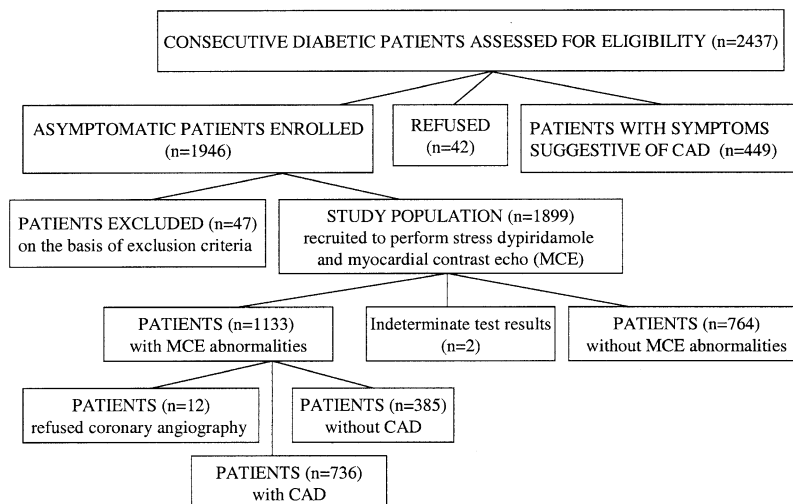


Figure 1. Flow chart of study population.

Before performing standard echocardiography, all patients had a venous blood sample for determination of the following parameters: hemoglobin (HbA), total, LDL- and HDL-cholesterol, triglycerides, glycemia, potassium, sodium, creatinine, aspartate-aminotransferase, alanine-aminotransferase, creatine phosphokinase, and HbA_{1c}. Other RFs for cardiovascular disease (CVD) were evaluated by history-taking. Values of other demographic parameters (age, gender, height/weight, and body mass index) at the moment of enrollment in the study were evaluated by searching the ambulatory clinical database. The presence/absence of retinopathy was documented both by a detailed and comprehensive eye examination and by the acquisition of high-quality stereoscopic photographs assessed by an ophthalmologist. Patients were tested for diabetic neuropathy (sensation to touch by monofilament, vibration sensation by tuning fork, and Achilles tendon reflex) and cardiac autonomic dysfunction (heart rate changes during deep breathing, the Valsalva maneuver, from lying to standing). Nephropathy was documented by the measurement of urinary albumin excretion (UAE): microalbuminuria was defined as UAE >30 μ g/min in at least three successive measurements, in the absence of other factors capable of causing proteinuria (urinary infection, glomerulonephritis, kidney stone, bladder cancer, etc.). Moreover, to document the possible presence of macrovascular disease, each subject was carefully characterized in terms of regional manifestations of atherosclerosis. A complete lifestyle questionnaire to obtain medical histories, parental history of CVD, information on smoking habits, and physical activity was filled in by the patients and individually checked. Peripheral vascular disease was considered if the ankle-brachial pressure index was 0.9 or less. A Doppler ultrasound of the carotid arteries was obtained in each patient to exclude significant carotid stenosis ($\geq 50\%$ luminal narrowing).

Finally, the study population consisted of 1,899 patients who were divided on the basis of the major RFs. Of these patients, 1,170 (62%) had ≥ 2 RFs for CAD (group A), and the remaining 729 had ≤ 1 RF for CAD (group B).

To detect myocardial perfusion abnormalities, all patients underwent a pharmacologic stress myocardial perfusion protocol including MCE at rest and during dipyridamole infusion. All DM2 patients with perfusion defects detected by MCE underwent coronary angiography at a mean of 9 ± 2 days after the noninvasive test. The study protocol was approved by the Ethical Committee of our University, and informed consent was obtained from all participants.

Echocardiographic analysis. Myocardial contrast echocardiography was performed at rest and during dipyridamole infusion (0.84 mg/kg body weight over 6 min), in apical four-, two-, and three-chamber view using an intermittent harmonic imaging with a phased-array system (Sonos 5500, Philips Medical System, Andover, Massachusetts) interfaced to an S3 transducer that transmits ultrasound at a mean frequency of 1.6 MHz and receives it at 3.2 MHz. Continuous venous infusion of a contrast agent (Levovist,

Schering AG, Berlin, Germany) was performed with an infusion pump (Medrad Pulsar, Indianola, Pennsylvania). Signal intensity was measured by acoustic densitometry in myocardial regions of the left ventricle and in the cavity. An intensity versus dose curve from the left ventricular cavity was plotted to obtain the dose where the relationship was linear. This dose was used in the contrast echocardiographic studies. Absence of any change in myocardial video intensity over five successive frames by visual assessment indicated the steady state. Once steady state was achieved, repeat imaging was obtained with sequential electrocardiogram triggering at end-systole. The pulsing interval was gated to the electrocardiograph and progressively increased from 80 ms to 10 s. Up to 12 images, acquired at each pulsing interval, were recorded on optical disk for quantitative analysis. Digitized studies were coded and read by two independent observers blinded to the patient's identity and the order of the study.

Background-subtracted myocardial signal intensity was plotted over the increasing pulsing intervals and fit to an exponential function as described by Wei et al. (18) for the determination of the rate constant (beta), which provides a measure of flow velocity, and the myocardial plateau intensity, which correlates with capillary cross sectional area and to myocardial blood volume (MBV). The product (beta \times MBV) represents a dimensionless index of myocardial blood flow (MBF) (19). During dipyridamole infusion, the myocardium subtended by $\geq 50\%$ coronary stenosis shows an attenuated hyperemic response (20), and both MBF and beta reserve decrease, as compared with myocardium subtended by no stenosis (21). Thus, MBF reserve (stress MBF/rest MBF) and beta reserve (stress beta/rest beta) were calculated. These parameters allow accurate detection of patients with CAD. A perfusion defect during dipyridamole infusion was diagnosed when MBF reserve was ≤ 1 and/or beta reserve ≤ 1.5 (15,16). In this study, the degree of interobserver and intraobserver correlations for measurements of MBV ($r = 0.94$ and $r = 0.96$, respectively) and beta ($r = 0.95$ and $r = 0.96$, respectively) was acceptable.

Coronary angiography. Selective coronary angiography was performed with the standard Judkins approach. All coronary angiograms were interpreted by two experienced physicians who were unaware of the contrast echocardiographic perfusion results. No cardiac events occurred in the interval between myocardial contrast echocardiographic study and coronary angiography. Significant CAD was defined as the presence of $\geq 50\%$ luminal diameter narrowing of one or more major epicardial arteries or its major branches. For CAD location, left main stenosis was regarded as disease of the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LCX). A "diffuse disease" was defined by the presence of significant stenosis in ≥ 2 coronary vessels with stenosis in ≥ 2 segments of each vessel.

Statistical analysis. Descriptive statistics were generated with percentages for discrete variables and mean \pm SD for

Table 1. Clinical Characteristics of the Study Population

	Group A (n = 1,170)	Group B (n = 729)	p
Age (yrs)	52.2 ± 7.0	52.0 ± 7.9	0.56
Men	67.3	67.9	0.49
BMI (kg/m ²)	29.2 ± 3.9	29.0 ± 3.5	0.26
HbA _{1c} (%)	8.3 ± 1.4	8.2 ± 1.9	0.19
Duration of the disease (yrs)	9.3 ± 6.0	9.4 ± 5.0	0.71
Major risk factors			
Current smoking	21.2	4.2	<0.001
Previous smoking	36.3	7.6	<0.001
Arterial hypertension	69.4	39.2	<0.001
Hypercholesterolemia	67.7	21.5	<0.001
Family history of premature CAD	28.7	6.4	<0.001
Microalbuminuria	37.3	6.4	<0.001
Other risk factors			
Retinopathy	8.2	8.7	0.82
Peripheral or carotid disease	5.6	2.6	<0.001
Medications			
Beta-blocker	35.0	18.1	<0.001
Calcium-channel blockers	25.2	24.8	0.96
ACE inhibitors	64.2	30.5	<0.001
ARB	19.4	19.2	0.95
Aspirin	54.5	42.2	<0.001
Statins	60.9	14.3	<0.001
Insulin	30.1	29.0	0.75

Results are expressed as mean ± SD or percentage (%). p values refer to comparisons between group A and group B patients.

ACE = angiotensin coenzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; Hb = hemoglobin.

normally distributed continuous variables. Continuous variables were compared between groups by means of the two-sample *t* test. A multivariate Cox proportional hazard regression model was used to determine if clinical characteristics were independently associated with significant CAD at coronary angiography. Regression analysis was performed for the major RFs (smoking, arterial hypertension, hypercholesterolemia, family history of premature CAD), body mass index (BMI), HbA_{1c}, duration of diabetes, retinopathy, and PVD. The number of coronary vessels and the presence of occlusion and of a “diffuse” disease were compared between groups with the chi-square test. A value *p* < 0.05 by the two-tailed test was considered statistically significant.

RESULTS

Clinical characteristics. Study groups were similar in age and gender (Table 1). In comparison with group B, group A patients had higher values of systolic blood pressure (154 ± 12 mm Hg vs. 147 ± 11 mm Hg, *p* < 0.001), diastolic blood pressure (95 ± 9 mm Hg vs. 89 ± 8 mm Hg, *p* < 0.001), total cholesterol (210 ± 35 mg/dl vs. 186 ± 40 mg/dl, *p* < 0.001), LDL cholesterol (140 ± 36 mg/dl vs. 115 ± 32 mg/dl, *p* < 0.001), and triglycerides (159 ± 80 mg/dl vs. 145 ± 82 mg/dl, *p* < 0.001). High-density lipoprotein cholesterol (55 ± 9 mg/dl vs. 54 ± 15 mg/dl, *p* = 0.069) did not differ significantly between study groups. Major risk factors for CAD as defined by the ADA Consensus Statement (17) were more common in group A

patients with DM2. As a consequence, the use of some medications (beta-blocker, angiotensin-converting enzyme inhibitors, aspirin, and statins) was more frequent in group A patients. The same percentage of patients in the two study groups used insulin. Body mass index, HbA_{1c}, and the incidence of retinopathy were similar, whereas group A patients had a higher incidence of peripheral or carotid artery disease.

MBF and coronary angiography. The percentage of diabetic patients with abnormal stress-MCE was similar in the two study groups with different RF profile (group A, *n* = 695, 59.4%; group B, *n* = 438, 60.0%). A significant CAD was present in 449 of 695 (64.6%) of group A and in 287 of 438 (65.5%) in group B patients (*p* = 0.92). Myocardial blood volume (5.2 ± 1.2 vs. 8.7 ± 1.0, *p* < 0.001), beta (0.34 ± 0.1 vs. 0.78 ± 0.3, *p* < 0.001), and MBF (2.2 ± 1.2 vs. 6.9 ± 2.9, *p* < 0.001) were significantly lower during dipyridamole than at rest in territories with significant CAD. In myocardial segments related to coronary vessels with <50% stenosis, MBV was similar during dipyridamole compared with rest (8.4 ± 0.9 vs. 8.5 ± 2.0, *p* = 0.14), whereas beta (1.5 ± 0.5 vs. 0.79 ± 0.4, *p* < 0.001) and MBF (16.2 ± 4.3 vs. 6.5 ± 2.3, *p* < 0.001) increased significantly. Multivariate analysis demonstrated that none

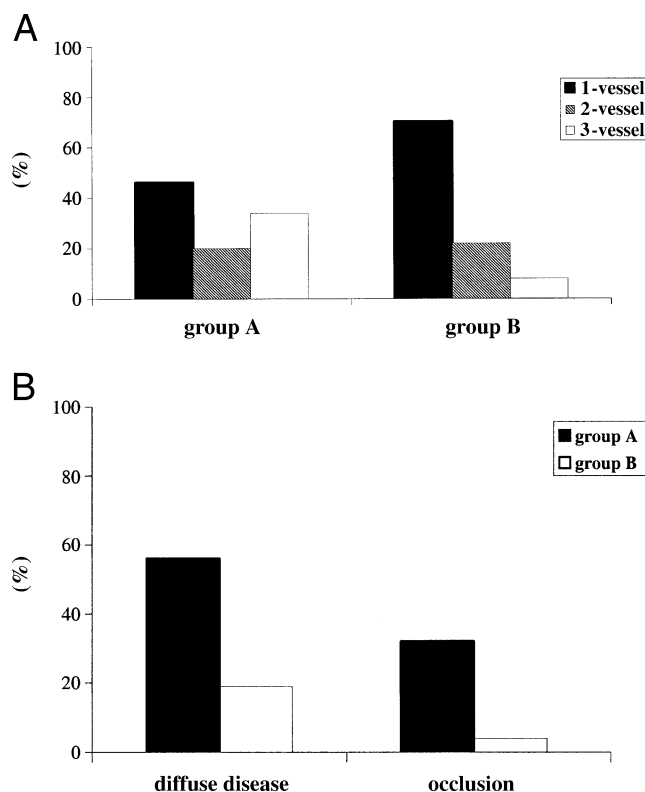


Figure 2. (A) Prevalence of one-, two-, or three-vessel coronary artery disease (CAD) in type 2 diabetes mellitus (DM2) patients with myocardial perfusion abnormalities at stress myocardial contrast echocardiography and two or more associated risk factors (RF) (group A) or no more than one RF (group B). (B) Prevalence of a “diffuse” coronary disease (defined by the presence of significant stenosis in two or more coronary vessels involving two or more segments of each artery) and of total occlusion in at least one epicardial vessel in group A and B patients with DM2.

of the clinical characteristics reported in Table 1 was an independent predictor of significant CAD at coronary angiography (smoking, $p = 0.72$; arterial hypertension, $p = 0.65$; hypercholesterolemia, $p = 0.24$; family history of premature CAD, $p = 0.45$), for BMI ($p = 0.82$), HbA_{1c} ($p = 0.72$), duration of diabetes ($p = 0.28$), retinopathy ($p = 0.57$), and for PVD ($p = 0.22$).

Angiographic characteristics of the coronary vessels and revascularization procedures. The angiographic characteristics of DM2 patients with abnormal MCE and different RF profiles are illustrated in Figure 2. Although the prevalence of overall significant CAD was similar in both groups (64.6% vs. 65.5%, $p = 0.81$), in group B, the percentages of patients with one-, two- and three-vessel disease were 70.6%, 21.8%, and 7.6%, respectively, significantly different from the pattern in group A (46.3%, 20.4%, and 33.3%, respectively, chi-square = 64.73, $p < 0.001$). Moreover, a larger percentage of group A patients had a “diffuse disease” (54.9% vs. 18.8%, chi-square = 93.83 $p < 0.001$) and an occlusion in at least one coronary vessel (31.2% vs. 3.5%, chi-square = 82.8, $p < 0.001$).

In addition, no consistent differences emerged between study groups regarding the sites of occluded vessels (LAD: 62.9% vs. 62.0%, $p = 0.65$; LCX: 8.0% vs. 8.9% $p = 0.79$; right coronary artery: 31.9% vs. 32.0%, $p = 0.81$).

Angiographic coronary anatomy did not allow any potential revascularization procedures (percutaneous coronary intervention [PCI]/coronary artery bypass grafting [CABG]) in 187 (41.6%) group A patients and in 32 (11.0%, $p < 0.001$) group B patients. Percutaneous coronary intervention was performed in 178 (39.6%) group A patients and in 122 (42.5%) group B patients. In coronary vessels treated by PCI, successful revascularization (residual coronary stenosis $<20\%$ and Thrombolysis In Myocardial Infarction flow grade 3) was obtained in 84% of procedures performed in group A and in 91% ($p < 0.001$) of procedures in group B. Sixty (13.3%) group A and 37 (11.4%) group B patients underwent CABG. Revascularization of all myocardial areas at risk was obtained in 44 (73.3%) group A patients and in 36 (97.2%) group B patients ($p < 0.001$).

DISCUSSION

In diabetic patients, the diagnosis of CAD generally is missed or delayed because the typical symptoms of cardiac ischemia are often masked. As a result, multivessel atherosclerosis often is present before ischemic symptoms occur and before treatment can be instituted (4). A delayed recognition of CAD undoubtedly worsens the prognosis for survival. Moreover, studies have shown that the absolute risk for major coronary events in patients with diabetes is similar to that of nondiabetic patients with established CAD and that diabetic patients who have not had a previous myocardial infarction have outcomes similar to those of patients without diabetes who have had a prior myocardial infarction (22). It follows that the combination

of CAD and diabetes mellitus is strongly indicative of adverse outcome and obliges clinicians to face up to the problematic issue of detection of CAD in individuals with no symptoms who have diabetes mellitus. Effective aggressive strategies for earlier detection of subclinical CAD could lead to more effective prevention and reduce morbidity and mortality. In this study, we investigated the prevalence of myocardial perfusion abnormalities and of CAD in adult (age ≤ 60 years) patients with type 2 diabetes.

To assess the role of associated major RFs for CAD, diabetic patients were divided into two groups with different RF profiles according to the recommendations of the ADA for test screening. The prevalence of myocardial perfusion defects and of CAD was similar in the study groups independently of RF profile, suggesting that a substantial number of asymptomatic diabetic patients with few RFs might have occult CAD. Together with the results of a recent study by Wackers et al. (23), these data demonstrate that several asymptomatic DM2 patients have myocardial perfusion abnormalities. The present study completed these observations by performing a coronary angiogram and also showed that the prevalence of significant CAD in patients with few RFs was similar to that of patients considered at high risk for CAD. These patients might be missed on the basis of current ADA guidelines (17). In addition, major RFs (smoking, arterial hypertension, hypercholesterolemia, family history of premature CAD, microalbuminuria) as well as retinopathy, PVD, HbA_{1c} , and duration of the disease did not emerge as significant predictors of myocardial perfusion abnormalities or significant CAD. Moreover, patients with CAD unmasked by an “aggressive” approach had a more favorable angiographic anatomy of coronary vessels. These latter patients had a lower prevalence of three-vessel disease, “diffuse disease,” and occlusion, whereas the prevalence of one-vessel disease was higher. These results are clinically relevant because angiographic coronary anatomy dramatically influenced the possibility to obtain adequate myocardial revascularization. Any potential procedure was contraindicated by coronary angiographic findings in about half of patients assigned to a conventional approach but only in a minority of cases in the subgroup in whom an aggressive approach was used. Moreover, when revascularization procedures were performed, group B patients obtained better results: a greater number of coronary vessels were successfully revascularized and, after CABG, almost all myocardial areas at risk were reperfused.

The study design of the present clinical investigation does not allow the assessment of the actual prevalence of CAD in asymptomatic patients with diabetes mellitus. There is no published large angiographic series of asymptomatic diabetic patients to address prevalence of CAD. In the largest autopsy study of diabetic patients without antemortem evidence of CAD, approximately 50% of patients <65 years of age and 75% of those ≥ 65 years of age had high-grade coronary atherosclerosis (24). By extrapolation, our series of patients seems to be representative of these data.

Myocardial hypoperfusion in diabetic patients might result from pathophysiological factors other than the epicardial coronary narrowing. These factors include small vessel disease, abnormal myocardial capillaries and small intramural arteries, endothelial dysfunction, increased platelet aggregability, and hyperfibrinogenemia (25-27). According to previous studies with different diagnostic approaches to detect myocardial ischemia or perfusion defects during stress, if coronary angiography is used as the gold standard (28-33), there is a subset of diabetic patients with a false positive stress myocardial contrast echocardiographic study. The data presented here contradict this perspective, suggesting that the diagnostic approaches to detect myocardial perfusion defects might be useful in asymptomatic diabetic patients with only microvascular disease in a subclinical stage. The microcirculation is an important target of diabetes mellitus, and myocardial perfusion defects might represent an early marker for deterioration in microvascular function, which plays a role in the pathogenesis of CAD. The response-to-injury hypothesis of atherosclerosis states that the initial damage affects the arterial endothelium, leading to endothelial dysfunction (34). Thus, myocardial perfusion defects in asymptomatic patients might represent an early marker for atherogenic process in the coronary circulation and might lead to a recommendation for an intensified multifactorial treatment approach (35) in these patients as well.

Conclusions and clinical implications. The patient population of the present study might be considered representative of asymptomatic DM2 patients followed in everyday diabetes practice. The findings of this study suggest that a substantial number of asymptomatic DM2 patients have myocardial perfusion defects and significant CAD independently from RF profile. As a consequence, a large number of asymptomatic DM2 patients with few RFs might have occult CAD and might be missed on the basis of current ADA guidelines (14,17). Moreover, patients with ≤ 1 RF, in whom an "aggressive" diagnostic approach was used, have a more favorable angiographic anatomy of coronary vessels. This might lead to an early aggressive medical treatment of CAD, and the more favorable coronary anatomy has rendered the coronary vessels of these diabetic patients more amenable to interventional treatment. Given the very high prevalence of myocardial perfusion defects and CAD in DM2 patients, this diagnostic approach could be more appropriate to the actual clinical decision-making process. In fact, diabetic patients have a risk for major coronary events similar to that of nondiabetic patients with established CAD and outcomes, in the absence of a previous myocardial infarction, similar to those of nondiabetic post-infarcted patients. In these latter patient groups, regular and routine stress testing is already universally considered as a standard approach. Contrarily, a high RF profile does not help to identify asymptomatic DM2 patients with a higher prevalence of CAD. In the context of DM2 patients with myocardial perfusion defects, a high RF profile is related to

a more severe CAD with an unfavorable angiographic anatomy limiting the possibility to perform a successful and complete revascularization by PCI or CABG. A subset of DM2 patients had myocardial perfusion defects in the absence of significant stenosis of coronary epicardial vessels, suggesting the potential to detect patients with only microvascular disease, which might constitute a very early phase of the atherogenic process in the coronary circulation. Thus, an aggressive diagnostic approach together with the previously recommended intensified multifactorial treatment approach in diabetic patients (35) has the potential to detect an early subclinical phase of the disease and lead to improvement in outcome of these patients. In 2008, all patients enrolled in the present study will complete a five-year follow-up, allowing an explanation of the effects of this diagnostic approach on the rate of cardiac events in asymptomatic DM2 patients. Moreover, the follow-up data will provide information for a correct economic analysis of this large-scale screening strategy.

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